Regulation of translation initiation by herpesviruses

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Abstract

Viruses are dependent upon the host cell protein synthesis machinery, thus they have developed a range of strategies to manipulate host translation to favour viral protein synthesis. Consequently, the study of viral translation has been a powerful tool for illuminating many aspects of cellular translational control. Although much work to date has focused on translational regulation by RNA viruses, DNA viruses have also evolved complex mechanisms to regulate protein synthesis. Here we summarize work on a large family of DNA viruses, the Herpesviridae, which have evolved mechanisms to sustain efficient cap-dependent translation and to regulate the translation of specific viral mRNAs.

Introduction

Herpesviridae

The Herpesviridae infect a wide range of vertebrates, including humans. They are composed of an icosahedral protein capsid containing a double-stranded linear DNA genome, of between 120 and 230 kb, that is enveloped by a lipid membrane with numerous glycoprotein spikes. Between the envelope and capsid is an amorphous layer, the tegument, which contains multiple virus-encoded proteins. Herpesviruses are divided into three subfamilies: the Alpha-, Beta- and Gamma-herpesvirinae. Eight herpesviruses, representing all three subfamilies, cause disease in humans (Table 1). For reviews of herpesvirus biology, see [1,2].

Although herpesviruses vary greatly in their biology and associated pathologies, they share key properties. Following primary infection, they establish latent infection, during which a very limited set of genes is expressed. However, viral reactivation results in a productive lytic replication cycle, characterized by a sequential co-ordinated gene expression programme. This is most extensively studied in HSV (herpes simplex virus) -1, where genes are divided into three classes: immediate-early (α or IE), delayed-early (β or E) and late (γ or L). Transcription of the IE genes, which encode regulatory proteins, does not require prior viral protein synthesis and is stimulated by the virion-associated transactivator VP16 (viral protein 16). Some IE proteins are required for expression of E and L genes, which mostly encode proteins necessary for DNA replication and virion assembly/maturatiom respectively. The L genes are subdivided into the leaky-late (L1) and true-late (L2) genes. Expression of the latter is absolutely dependent upon viral DNA replication [1].

Herpesvirus mRNAs are transcribed by cellular RNA polymerase II and are capped and polyadenylated, but predominantly intronless. To facilitate virus gene expression, HSV-1 infection induces a rapid inhibition of host gene expression; initially via indiscriminate degradation of mRNA by the virion-associated host shut-off (vhs) protein [3] and later via inhibition of splicing by the IE protein ICP (infected cell protein) 27 [4,5] and transcriptional shut-off via altered RNA polymerase II phosphorylation [6]. These activities drastically reduce competition with host transcripts for the cellular translation machinery, and, consequently, the virus has evolved mechanisms to maintain efficient cap-dependent translation of viral mRNAs rather than incapacitating this process. In the present article, we review a number of studies, focusing on HSV-1, which indicate that herpesviruses modulate several components of the cellular translational machinery to maintain active protein synthesis. We also discuss recent data suggesting that a viral regulatory protein may activate directly the translation of a subset of viral mRNAs.

Initiation of translation

Eukaryotic mRNA translation is a highly regulated process that occurs in three phases: initiation, elongation and termination. In initiation, ribosomal subunits and Met-tRNA, (initiator methionyl-tRNA) are recruited to mRNAs to enable elongation, during which mRNAs are decoded to produce a polypeptide. Termination is triggered upon encountering a stop codon, resulting in release of polypeptide
the first mRNA-dependent step is the binding of a complex of pre-initiation complex. In contrast with the later steps, these early steps do not occur on mRNA. In cap-dependent initiation, the presence of these structures functionally link the ends of mRNAs and the cap and poly(A) tail function as the primary determinants of efficient cap-proximal secondary structure within the 5′-UTR (untranslated region) before 43S complex binding. 43S complex recruitment is also facilitated by interaction of eIF3, part of the 43S complex, with eIF4G. Once recruited, the 43S complex and associated factors 'scan' along the 5′-UTR until an appropriate initiator codon is located. AUG recognition by Met-tRNAi, promotes the hydrolysis of eIF2-bound GTP, the dissociation of initiation factors and the joining of the 60S ribosomal subunit. Surprisingly, the 3′-end poly(A) tail also contributes to initiation via its associated protein PABP [poly(A)-binding protein]. Interactions between PABP and the eIF4F complex functionally link the ends of mRNAs and the cap and poly(A) tail function as the primary determinants of efficient cap-dependent initiation [10]. The presence of these structures in herpesviral mRNAs, along with its other mechanisms for reducing host competition, may explain why these viruses, in contrast with a variety of well-studied RNA viruses [11], preserve this cap-dependent pathway during infection.

Regulation of translation can be 'global', causing widespread effects of varying magnitude on many mRNAs, or 'specific', affecting a single or subset of mRNAs. Global control is normally achieved by changes in the activity of basal components of the translational machinery [8], whereas mRNA-specific regulation is normally directed by cis-acting regulatory elements that sometimes serve as binding sites for trans-acting factors [7]. In responding to a particular event, re-programming of cellular protein synthesis may involve global and mRNA-specific regulation. Defects in both types of control are associated with disease [12,13]. Both global and mRNA-specific regulation frequently target the eIF4 group of initiation factors and the recycling of eIF2 [7,14]. For instance, the 4E-BP (eIF4E-binding protein) family down-regulates general cap-dependent translation in response to a variety of environmental cues by binding to eIF4E and preventing its interaction with eIF4G, thus reducing the levels of eIF4F available for initiation [15]. A similar strategy is utilized to achieve mRNA-specific regulation by 4E-BP-like proteins associated with specific mRNAs [15]. Other components of the eIF4F complex are also subject to complex regulation [16,17]. Regulation of eIF2 is achieved primarily by phosphorylation of Ser-51 on the α-subunit, which is targeted by a number of signalling pathways in response to a variety of stresses, including amino acid starvation, viral infection, ER (endoplasmic reticulum) stress and oxidative stress [11,18]. This phosphorylation interferes with the recycling of eIF2-GDP to eIF2-GTP by the GEF (guanine-nucleotide-exchange factor) eIF2B, and leads to depletion of ternary complex. The high affinity of phosphorylated eIF2-GDP for eIF2B causes accumulation of blocked eIF2-GDP-eIF2B complexes [11,18] (Figure 2A). Since eIF2B is present at relatively low levels, phosphorylation of moderate amounts of eIF2α can drastically reduce translation.

### HSV-1 response to translational control by cellular eIF2α kinases

Cells respond to viral infection by secreting interferons to elicit antiviral responses in neighbouring cells by inducing expression of interferon-stimulated genes, including PKR [dsRNA (double-stranded RNA)-dependent protein kinase], a key regulator of protein synthesis. PKR is activated by intermolecular autophosphorylation when bound to dsRNA of sufficient length or via the stress-induced PACT (protein activator of PKR). Activated PKR phosphorylates eIF2α and reduces global translation by impeding ternary complex formation (Figure 2A) [11].

### Table 1 | Human herpesviruses

<table>
<thead>
<tr>
<th>Name</th>
<th>Subfamily</th>
<th>Genome size (kb)</th>
<th>Common disease/symptoms</th>
</tr>
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<tbody>
<tr>
<td>HSV-1</td>
<td>α</td>
<td>152</td>
<td>Cold sores</td>
</tr>
<tr>
<td>HSV-2</td>
<td>α</td>
<td>152</td>
<td>Genital lesions</td>
</tr>
<tr>
<td>VZV (also known as HHV-3)</td>
<td>α</td>
<td>125</td>
<td>Chickenpox/ shingles</td>
</tr>
<tr>
<td>EBV (also known as HHV-4)</td>
<td>γ</td>
<td>172</td>
<td>Infectious mononucleosis (glandular fever), Burkitt’s lymphoma and other cancers</td>
</tr>
<tr>
<td>HCMV (also known as HHV-5)</td>
<td>β</td>
<td>229</td>
<td>Mononucleosis</td>
</tr>
<tr>
<td>HHV-6</td>
<td>β</td>
<td>162</td>
<td>May be associated with progression of AIDS</td>
</tr>
<tr>
<td>HHV-7</td>
<td>β</td>
<td>145</td>
<td>None known</td>
</tr>
<tr>
<td>KSHV (also known as HHV-8)</td>
<td>γ</td>
<td>170</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>
**Figure 1 | Cap-dependent initiation of translation**

The model shown is consistent with the majority of data available for metazoans (reviewed in [9]). Steps known to be subject to regulation by herpesviral proteins are depicted by red arrows. eIFs are represented by their number, ribosomal subunits by 40S and 60S, Met-tRNA is identified by Met and mRNA by the AUG start codon. Representation of complexes is purely schematic. (A)-(C) mRNA-independent steps. 

(A) Ribosomal subunits are dissociated, and free 40S subunits associate stably with eIF3 and with eIF1 and eIF1A which aid dissociation. (B) eIF2-GDP is regenerated to eIF2-GTP by the action of eIF2B and is then available for interaction with Met-tRNA, to generate the ternary complex. (C) Ternary complex is recruited to the 40S subunit to form the 43S pre-initiation complex. (1)-(6) mRNA-dependent steps. (1) The eIF4F cap-binding complex is recruited to the 5′ cap via the cap-binding protein eIF4E. eIF4G co-ordinates the binding of eIF4E to the cap and the helicase activity of eIF4A, and also binds RNA and eIF3. (2) The eIF4F complex facilitates the unwinding of cap-proximal secondary structure (shown as stem-loop) by the action of the ATP-dependent RNA helicase eIF4A, stimulated by its closely associated co-factor eIF4B. (3) Unwinding allows the 43S pre-initiation complex to join the mRNA near the cap. Multiple interactions including an interaction between eIF4G and eIF3 probably facilitate this step. (4) The 43S complex rearranges and ‘scans’ the 5′-UTR to locate an appropriate start codon in an ill-defined process, during which unwinding of secondary structure is coupled to ribosome movement. It is not clear when interactions between the cap, eIF4F and the 43S complex are disrupted. (5) AUG recognition is driven primarily by complementarity with the anticodon of the Met-tRNA, but is influenced by factors including eIF1, eIF1A and eIF2. Completion of eIF2-GTP hydrolysis by the GTPase-activating protein eIF5 destabilizes interactions, and initiation factors are released by the combined action (6) of a ribosome-dependent GTPase eIF5B and the joining of the 60S subunit. Initiation ends with the Met-tRNA based paired with the initiation codon of the mRNA in the P-site of the 80S ribosome, with the A-site being available for delivery of tRNA. The poly(A) tail and its associated protein, PABP, have pleiotropic effects on initiation which are not depicted and may also aid recycling of subunits for subsequent rounds of initiation [10].

**Figure 2 | Maintenance of cap-dependent translation during HSV-1 infection**

(A) Regulation of ternary complex. eIF2-GDP is exchanged for eIF2-GTP in order to regenerate ternary complex for initiation. This is achieved by the GEF eIF2B. During viral infection, phosphorylation of the eIF2α subunit can be driven by PKR or PERK activation. eIF2 can be dephosphorylated by PP1. Phosphorylated (depicted by a circled P) eIF2-GDP interacts in a stable manner with eIF2B, preventing recycling to eIF2-GTP and sequestering eIF2B, which is present in rate-limiting amounts. During early HSV-1 infection, accumulation of phosphorylated eIF2 is prevented by the stimulation of PP1 by ICP34.5, whereas, later, US11 blocks the activation of PKR. gB is suggested to interfere with PERK action. (B) Regulation of eIF4F. eIF4E binding to eIF4G to form eIF4F complexes (which also contain eIF4A) is blocked by hypophosphorylated 4E-BPs, which compete for the same binding site on eIF4E. Phosphorylation of 4E-BP by mTOR–raptor during viral infection releases eIF4E, making it available for interaction with eIF4G as part of the eIF4F complex. eIF4E-eIF4G interactions can also be stimulated by the eIF4G-interacting protein ICP6 in infected cells. In this way, ICP6 may also indirectly promote phosphorylation of eIF4E which is directed by the eIF4G-associated kinase Mnk-1.
HSV-1 infection produces dsRNA, which activates PKR, especially at later times of infection, presumably due to transcription of overlapping genes on opposing DNA strands [19,20]. However, HSV-1 encodes two sequentially expressed proteins, ICP34.5 (L1) and US11 (L2), that are both required to counteract PKR-mediated translational shut-off [11,21,22]. ICP34.5 has homology with the cellular protein GADD34 (growth-arrest and DNA-damage-inducible protein 34) which is a regulatory subunit of a PP1 (protein phosphatase 1)-containing complex that dephosphorylates eIF2α during recovery from ER stress [23]. Like GADD34, ICP34.5 stimulates cellular PP1 to prevent accumulation of phosphorylated eIF2α [24,25]. Subsequently, PKR activation can be inhibited by US11, which has also been suggested to block eIF2 phosphorylation by activated PKR [26–29]. A region within US11, containing multiple Arg-Xaa-Pro repeats, appears to mediate dsRNA, PKR and PACT binding, and is sufficient to inhibit PKR activation [27,29], but its mechanism of action remains unknown.

ER stress results in eIF2 phosphorylation via PERK (PKR-like ER kinase) and can occur in infected cells owing to ER overloading with virus-encoded proteins [11]. Recent reports show that the early viral gB (glycoprotein B) associates with the luminal domain of PERK [30]. Genetic evidence suggests that gB may interfere with PERK-mediated translational regulation independently of ICP34.5 and US11 and may modulate the ER stress response [30,31].

Factors encoded by other herpesviruses to prevent eIF2α phosphorylation

Herpesviruses from the β and γ subfamilies also overcome the antiviral PKR response. HCMV (human cytomegalovirus), a betaherpesvirus, encodes two factors, TRS1 and IRS1, which restore protein synthesis in an ICP34.5-deficient HSV-1 virus [32]. The functional mechanism has not been fully elucidated, but, for TRS1, it may involve relocalization of PKR to the nucleus [33]. During latency, the gammaherpesvirus EBV (Epstein–Barr virus) expresses the non-coding EBER (EBV-encoded RNA)-1 and EBER-2 which bind to PKR and, during lytic infection, expresses the Sm protein which shares encoded RNA)-1 and EBER-2 which bind to PKR and, (Epstein–Barr virus) expresses the non-coding EBER (EBV-nucleus [33]. During latency, the gammaherpesvirus EBV [32]. The functional mechanism has not been fully elucidated, restores protein synthesis in an ICP34.5-deficient HSV-1 virus betaherpesvirus, encodes two factors, TRS1 and IRS1, which antiviral PKR response. HCMV (human cytomegalovirus), a betaherpesvirus, encodes two factors, TRS1 and IRS1, which restore protein synthesis in an ICP34.5-deficient HSV-1 virus [32]. The functional mechanism has not been fully elucidated, but, for TRS1, it may involve relocalization of PKR to the nucleus [33]. During latency, the gammaherpesvirus EBV (Epstein–Barr virus) expresses the non-coding EBER (EBV-encoded RNA)-1 and EBER-2 which bind to PKR and, during lytic infection, expresses the Sm protein which shares homology with the Arg-Xaa-Pro repeat of HSV-1 US11. EBER RNAs and Sm all inhibit PKR activation in vitro [34,35]. KSHV (Kaposi’s sarcoma-associated gammaherpesvirus) vIrf-2, a latently expressed homologue of cellular interferon-regulatory factors, counteracts interferon-induced translational inhibition by interacting with PKR and inhibiting its activation [36]. Thus different herpesviruses appear to use generally unrelated factors to solve the same problem.

Herpesviruses affect the assembly and modification of eIF4F

Phosphorylation of 4E-BPs and assembly of eIF4F by HSV-1

Hypophosphorylated 4E-BPs bind to eIF4E, preventing eIF4F complex formation (Figure 2B). 4E-BPs are substrates of the cellular mTOR (mammalian target of rapamycin) kinase, and 4E-BP hyperphosphorylation strongly reduces their affinity for eIF4E, enabling assembly of eIF4F complexes. Activated mTOR functions in two distinct complexes, containing either raptor (regulatory associated protein of mTOR) or rictor (rapamycin-insensitive companion of mTOR) protein, which have different specificities, and 4E-BPs are hyperphosphorylated by the rapamycin-sensitive mTOR–raptor complex (reviewed in [8]).

HSV-1 infection of primary fibroblasts induces mTOR-dependent phosphorylation and proteasome-mediated degradation of 4E-BP [37]. Both of these effects are dependent on expression of unidentified viral protein(s) (Figure 2B) [37,38]. Perhaps surprisingly, a concomitant increase in eIF4G-containing cap-binding complexes was observed only in serum-starved (quiescent) cells, but this may be due to differing translation rates and eIF4F levels in cycling compared with quiescent cells [37]. As HSV-1 is latent in quiescent neurons, the authors suggest that this increase in eIF4F might reflect an adaptation to allow efficient protein synthesis upon reactivation [37,38].

However, the induction of eIF4F formation in quiescent cells is only partially sensitive to rapamycin [37], implying that HSV-1 employs an additional mechanism to enhance eIF4F assembly. Recent work suggests that the HSV-1 ICP6 protein, a subunit of ribonucleotide reductase, may play a role. In cells infected with an ICP6-deficient virus, eIF4G appears inefficiently recruited to the eIF4F complex, despite degradation of 4E-BP [38]. ICP6 apparently associates with eIF4F complexes via the N-terminus of eIF4G, stimulating eIF4G binding to eIF4E in infected cells and in the absence of other viral proteins in vitro [38]. ICP6 contains a region homologous with small heat-shock proteins and the corresponding HSV-2 protein exhibits chaperone activity in vitro [39]. However, it remains to be determined whether chaperone activity contributes to its modulation of eIF4F.

Phosphorylation of eIF4E by HSV-1

eIF4E is phosphorylated by the cellular eIF4G-associated Mnk-1 kinase which acts downstream of p38 and ERK (extracellular-signal-regulated kinase) MAPKs (mitogen-activated protein kinases), but the role of eIF4E phosphorylation on cellular translation remains unclear (reviewed in [8,40]). HSV-1 infection of primary human cells leads to p38- and Mnk-1-dependent (but ERK-independent) accumulation of eIF4E phosphorylation [37]. Treatment of quiescent cells with a specific Mnk-1 inhibitor reduces viral yield 100-fold, indicating that Mnk-1 is important, at least in growth-arrested cells. Indeed, under the same conditions, inhibition of 4E-BP phosphorylation by rapamycin reduced viral replication only 2-fold [37]. eIF4E phosphorylation requires viral gene expression [37,38], and at least one HSV-1 protein, ICP27, has been implicated in p38 activation [41,42]. In addition, ICP6, although dispensable for p38 activation, is required for efficient eIF4E phosphorylation perhaps because, in its absence, insufficient eIF4G-associated Mnk-1 is recruited to the cap-binding complex (Figure 2B) [38].
The contribution of Mnk-1 to natural infection remains to be determined, since the effect of Mnk-1 inhibition is only apparent in quiescent cells at low multiplicities of infection [37]. Furthermore, the extent to which Mnk-1 acts via changes in eIF4E phosphorylation, and the extent to which this contributes to HSV-1 translation awaits clarification.

**eIF4F assembly and phosphorylation by other herpesviruses**

Regulation of eIF4F assembly is not unique to alphaherpesviruses. Infection with HCMV also induces eIF4E phosphorylation, but, in contrast with HSV-1, this unusually appears to involve both mTOR–raptor and mTOR–rictor [43–45]. During latent infection, EBV expresses a membrane protein LMP2A (latent membrane protein 2A), which activates mTOR and leads to 4E-BP phosphorylation [46]. HCMV infection also stimulates eIF4E phosphorylation, and HCMV replication in quiescent human cells is extremely sensitive to Mnk-1 inhibition. However, in contrast with HSV-1, Mnk-1 activation in HCMV-infected cells is both p38- and ERK-dependent [44]. Furthermore, an increase in the abundance of eIF4E and eIF4G is seen during infection of quiescent cells with HCMV, but not HSV-1 [37,44]. This is accompanied by an increase in PABP levels and its association with eIF4F [44]. Less is understood about the translational consequences of these changes in beta- and gamma-herpesviruses, and, for the most part, the viral activities involved in these modifications have yet to be identified.

**Translational control by the HSV-1 ICP27 protein**

The modulation of eIF4F and eIF2 would be expected to provide a cytoplasmic environment primed for efficient viral translation. In addition to these global effects, recent evidence indicates that the HSV-1 ICP27 directs mRNA-specific regulation. ICP27 is an essential IE phosphoprotein with counterparts in all sequenced mammalian and avian herpesviruses [47]. This multifunctional nucleocytoplasmic-shuttling RNA-binding protein regulates gene expression predominantly post-transcriptionally, for example by inhibiting host cell splicing and promoting nuclear export of viral transcripts [4,5]. However, the requirement for ICP27 in nuclear export is mRNA-specific, as some viral mRNAs, such as that encoding the L protein VP16, accumulate in the cytoplasm independently of ICP27 in infected cells [48,49]. Nevertheless, VP16 protein synthesis is dramatically reduced after infection with a mutant virus lacking ICP27 compared with wild-type virus. This is reflected in a loss of VP16 mRNA from polyribosomes, suggesting a role for ICP27 in regulating its translation [49]. ICP27 itself was subsequently shown to be associated with polyribosomes in infected cells [50], suggesting that its role in VP16 mRNA translation may be direct. This hypothesis was examined using a tethered-function approach [51] which revealed that ICP27 has the capacity to stimulate translation directly and efficiently [50]. However, in contrast with the regulation described above, ICP27 activates only the translation of mRNAs to which it is bound, suggesting a role in mRNA-specific rather than global translation [50]. Support for a role in mRNA-specific translation was also obtained in virally infected cells, since translation of ICP5 as well as VP16 mRNA, but not tk (thymidine kinase), ICP8 and gD (glycoprotein D) mRNAs, is diminished in the absence of ICP27 [49,52].

The mechanism by which ICP27 stimulates these mRNAs remains to be determined; however, tethered ICP27 can efficiently activate translation in a heterologous system, suggesting that it is sufficient to mediate translational stimulation in the absence of other viral proteins [50]. Thus it is likely that the ICP27 binds directly or indirectly (via other cellular partners) to a component of the cellular translational machinery. This factor may have a role in initiation, since the redistribution of VP16 mRNA from polysomes to lighter complexes, in the absence of ICP27, is indicative of a reduced initiation rate [49]. Intriguingly, an association of ICP27 with complexes containing two initiation factors, PABP and eIF3 (see legend to Figure 1), has been reported [53]. However, this may represent fortuitous co-isolation via mRNA, as these interactions are highly ribonuclease-sensitive and any functional significance remains to be determined [53]. Translational stimulation by tethered ICP27 requires the C-terminal region of the protein, and point mutations within this conserved domain abolish translational stimulation in tethered-function assays and abrogate polyribosome association of ICP27 in infected cells [50]. This suggests that this region may interact functionally with components of the initiation machinery, and it has been observed that mutant viruses expressing C-terminally truncated forms of ICP27 fail to stimulate VP16 translation during viral infection [52]. Thus stimulation of translation is probably achieved through proteins interacting with this region, and a clear priority is to determine whether eIF3, PABP or other initiation factors interact directly with ICP27, particularly its C-terminus.

The specificity of this regulation probably reflects the binding of ICP27 to a subset of viral mRNAs in the cytoplasm. It remains possible that other viral proteins may aid ICP27 binding to mRNA or alter its target specificity, and the regulatory elements bound by ICP27 (and its partners) that mediate translational effects remain to be identified. Although it is tempting to speculate that ICP27 may leave the nucleus bound to these mRNAs, further work is required to establish the extent to which ICP27 accompanies its translational targets into the cytoplasm. However, the multifunctional nature of ICP27 complicates such analyses. A fuller understanding of the target mRNAs of this regulation will be important in determining the extent and importance of this new role of ICP27 to the viral life cycle.

**Future directions**

The translational activation of specific mRNAs by ICP27 provides a new facet to translational regulation by herpesviruses. This novel function may be a conserved feature of this family as ICP27 has homologues in all other herpesviruses.
To date, only a handful of mRNA-specific RNA-binding proteins that activate translation have been identified, and their mechanism of action has only been studied in a few cases. Several of these factors that play a specialized role in IRES (internal ribosome entry site)-mediated translation, an alternative initiation pathway [54]. However, no IRESs have been reported in the identified ICP27 mRNA targets, and cap-dependent translation is not compromised during HSV-1 infection. Although the eIF4F complex appears to be targeted by other studied activators (e.g. [55,56]), it is currently unclear whether they provide a model for ICP27 function. Thus further study of ICP27 may provide the paucity of models available for understanding the action of mRNA-specific activators. Identification of the cellular factors targeted by ICP27 will provide insights, but ultimately a molecular understanding of how these interactions stimulate one or more steps in the initiation pathway will be required.

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